DRUG DEVELOPMENT COMMUNICATIONS, 2(4&5), 429-438 (1976)

DRUG DISSOLUTION TESTING: TODAY AND TOMORROW

James Swarbrick, Sterling-Winthrop Research Institute,
Rensselaer, N.Y. 12144

ABSTRACT

This article discusses the present role of dissolution tests both in terms of current compendial requirements and the use of such tests by the pharmaceutical industry.

Insofar as future use is concerned, the suggestion is made that the compendia clearly distinguish between those monographs where dissolution tests have been shown to be of biological significance (i.e., Digoxin Tablets) and those which are simply acting as physical quality control procedures. Logically, a dissolution test should be applied to all solid dosage forms, although from a logistical point of view it might be appropriate to confine this requirement, at least initially, to those drugs having an aqueous solubility of 0.5 per cent or less.

In the future, the pharmaceutical industry should expand its use of dissolution testing both in formulation development and production control, with a view to establishing, in as many instances as possible, dissolution tests having biological

significance, i.e., where reliable *in vitro* - *in vivo* correlations have been established.

With the realization that drugs must be in solution in order to be absorbed from the gastrointestinal tract, and that the rate and extent of bioavailability can often be controlled by the rate of drug dissolution, it is not surprising that increasing emphasis is being given to the design and utilization of *in vitro* dissolution tests and procedures. Dissolution, like any new procedure, has had to go through a period when the value attached to it varied widely over relatively short intervals of time. Thus, dissolution testing has been regarded by some as a total waste of time and by others as the total panacea, capable of replacing completely the need to conduct *in vivo* availability tests of products in man. At the present time, it would appear that dissolution testing has now been around long enough so that a proper assessment of its current utility and some reasonable projections for the future can be made.

DEVELOPMENT OF DISSOLUTION TESTING

In reviewing the background to dissolution testing, it is apparent that up to the mid-1950's disintegration was the key word used in discussing the formulation of solid dosage forms. Either those working in the area were unaware of the need for a drug to dissolve before being absorbed - which is doubtful - or they simply regarded the act of disintegration as being synonymous with drug absorption. Only with the development of sustained release dosage forms just over twenty years ago, did pharmaceutical

scientists start to realize, at least in print, that a dissolution test was necessary in order to determine the release pattern of a drug from a dosage form. It then became obvious that the compendial disintegration tests had very little relevance to dissolution and that other forms of standardized tests needed to be developed in order to better assess drug dissolution from a formulation.

Over the past twenty years there has been a virtual explosion of dissolution methods developed and published. A great number are of limited value only, in that no attempts were made to correlate the dissolution data with drug bioavailability. This is unfortunate, since the ultimate objective of the dissolution test should be to establish this correlation. If a correlation cannot be shown to exist, then such should be clearly stated so that dissolution tests can begin to be classified into one of two categories, namely: (1) a dissolution test having biological significance, in that satisfactory *in vitro - in vivo* correlation exists, and (2) a dissolution test of simply *physical* significance, where, although such a correlation has not been demonstrated, an adequate amount of drug is released from the dosage form under a set of arbitrary *in vitro* conditions. This separation of dissolution tests and specifications into two such distinct categories is seen as a necessary and logical future step.

Turning now to the situation today in terms of dissolution testing and requirements, three groups with an interest in dissolution testing are the official compendia, the pharmaceutical industry, and the Food and Drug Administration. While this

presentation concentrates on the first two of these, impending regulations on bioavailability, bioequivalence and government drug reimbursement programs make it apparent that FDA's involvement in this area of *in vitro* testing will increase in the future.

DISSOLUTION AND THE COMPENDIA

The USP and NF both introduced dissolution tests several years ago, and the view subsequently developed that compliance with the specifications would ensure adequate bioavailability and bioequivalence for the products so named. The statements in the compendia did contribute, in part, to this assumption. Thus, according to the USP XVIII (page 934), "The dissolution test affords an objective means of determining the dissolution characteristics of a solid dosage form. Since drug absorption and physiological availability are largely dependent upon having the drug in the dissolved state, suitable dissolution characteristics are an important property of a satisfactory drug product."

That statement, which appears to imply some degree of correlation betweer the dissolution specifications and *in vivo* availabili:y, still apears in USP XIX (page 651) even though there is no published evidence that shows correlation of the dissolution specifications with *in vivo* availability for those drugs that have dissolution tests in their monograph, with the notable exception of Digoxin. The statements within NF XIV (page 941) are also still somewhat ambiguous in that they too tend to imply that correlation exists between the specifications for dissolution and bioavailability

for the several monographs that contain such specifications.

Unfortunately, this implication is strengthened, by the selective inclusion of the dissolution test in certain monographs. The only instance where correlation has been demonstrated is with the new test for Digoxin Tablets, where now the statement is made in USP XIX that the "new dissolution test for Digoxin Tablets is particularly significant because the rate of dissolution for this article has been shown to correlate closely with the bioavailability of the article."

It would seem to be better, therefore, to clarify the situation with a statement that, apart from Digoxin Tablets, the current compendial dissolution tests are not meant to, nor do they, correlate with in vivo availability. Compliance by a formulation meeting the monograph specifications with respect to dissolution simply means that a required physical property of the dosage form is confirmed. The only test and specification that may be properly related with bioavailability, and which is thus a biological control procedure, is that for Digoxin Tablets.

The fact that the great majority of compendial dissolution tests are in the nature of physical, rather than biological, controls should not detract from the significance of such tests. In the sense that dissolution is necessary before absorption can occur, whereas disintegration is not, the significance of even a physical dissolution test is far greater than that of the disintegration test which is applied to all oral tablets.

DISSOLUTION AND THE PHARMACEUTICAL INDUSTRY

Increasingly, the major task of any modern product development group is to optimize and control the delivery of the drug from the dosage form. This requires a comprehensive knowledge of the dissolution and absorption properties of the drug, together with an appreciation of the effect of all other components present on these properties. The main objectives behind dissolution testing are as follows. First, within a product development group, dissolution testing should be used as a tool to confirm that the dosage form developed does not compromise the inherent dissolution of the active compound. Second, this group should also be striving to develop meaningful correlations between *in vitro* dissolution and *in vivo* availability. Third, in the production area, dissolution testing should be applied routinely to monitor batch-to-batch variation in the quality control of the product.

There is little doubt that most companies undertake dissolution studies on a new drug moiety during preformulation work. Generally, this can be easily achieved using a simple compress and a procedure such as the rotating disc or beaker method. Such basic information is of prime importance to the formulator who should be able to defend both the choice and level of any and all components incorporated into a dosage form. Having a simple dissolution method available during development of the formulation, plus preformulation information on the compound's dissolution under a variety of pH and particle size conditions, simplifies the formulator's task to the point where

one of his main objectives is not to compromise the inherent rate of dissolution of the pure compound. Other considerations include maintaining physical and chemical stability of the formulation and facilitating production.

Turning now to in vivo - in vitro correlations, the FDA will require bioavailability studies for new products which have not been previously marketed and are therefore the subject of an NDA submission. It is logical under these circumstances to undertake strong efforts to develop in vivo - in vitro correlations. Unfortunately, the number of instances where such data have been well developed are few. In order to properly develop such correlations, a multiple point relationship must be established, in which formulations having both good and poor dissolution characteristics are run in man in order to seek good and poor absorption data. It is doubtful if more than a very few companies conduct bioavailability studies with a range of formulations in order to assess these parameters. Thus, the sensitivity of the dissolution test in being able to differentiate between various levels of bioavailability is hardly ever established - yet this is a prerequisite to establishing meaningful correlations.

In the case of non-prescription or OTC drug products, involving known and previously marketed drugs and drug combinations, the amount of published bioavailability work is also sparse. This too is an area in which in vivo - in vitro correlations could and should be established, both to commercial and scientific advantage.

In the production area, dissolution testing has an important role to play in the control and release of product and the following of batch-to-batch variations. Here too it is unlikely if the majority of companies know the significance and sensitivity of any dissolution data they obtain on production batches of product. It is likely that the meaning of changes in dissolution as a result of batch-to-batch variation, long term stability and ageing is neither appreciated nor understood. These effects, plus a total knowledge of the effect of processing factors, are areas where expanded research efforts are needed and the publication of results encouraged.

THE FUTURE OF DISSOLUTION TESTING

What of tomorrow ? First, what more can we expect of dissolution testing from the compendia ? Is it not time to see the institution of a dissolution specification for all tablets, capsules and suppositories ? Surely it is illogical to persist in carrying out disintegration tests while not requiring evaluation of drug dissolution ? The test could be simple, using one method, and with the minimum of variations in terms of solvent, agitation intensity, and pH. The compendia should acknowledge that these dissolution tests would simply be physical quality control procedures with no implication whatsoever that conformance guarantees or even suggest an adequate bioavailability or acceptable bioequivalence. The compendia would only be requiring confirmation that under a given set of in vitro conditions a certain fraction of the drug can escape from the dosage form - arbitrary informa-

tion to be sure but valuable in assessing product performance by *in vitro* means.

As a reasonable first step, a start could be made on all those product monographs containing drugs whose solubility is 0.5 per cent or less. This would also require a complete list of solubilities being developed by the compendia, something which in itself would be desirable. A check through the list of solubilities published in USP XIX shows that for those drugs having a dissolution test, only sulfisoxazole has a solubility quoted. At the same time biological dissolution specifications should be established in as many monographs as possible, but only when adequate correlation has been demonstrated using whatever method is found to work. Initially, therefore, all tablets, capsules and suppositories would have a physical dissolution test utilizing one dissolution method. When adequate *in vivo* - *in vitro* correlation was demonstrated, as for example with Digoxin Tablets, then the physical dissolution specifications would be replaced by biological dissolution specifications. It would seem that this "two level" approach is a far more logical way of developing and utilizing dissolution specifications within the compendia.

Insofar as the future of dissolution testing within the pharmaceutical industry is concerned, quite obviously it should be used more frequently in product development groups. In particular, greater emphasis must be placed on developing multiple point correlations between the dissolution of formulations and their *in vivo* availability.

There is also a need for a greater understanding of processing factors, storage conditions and ageing on bioavailability, and how dissolution testing can be used to monitor such changes.

In conclusion, the development of meaningful dissolution tests is still complicated, in a state of relative infancy insofar as biological significance is concerned and requires increased attention and resources. Nevertheless, the expansion of dissolution testing and the development of appropriate dissolution specifications are worthwhile endeavours, provided the limitations are realized. In terms of a purely physical specification, dissolution testing is a valuable adjunct to good formulation development. On a biological level, the establishment of an adequate correlation provides an excellent tool with which to monitor the consistency of drug delivery from a product. Both of these are desirable goals for any product development group today - and tomorrow.

NOTES

This paper is based, in part, on a presentation to the APhA Academy of Pharmaceutical Sciences meeting, San Francisco, April, 1975.

Present address: Department of Pharmacy,
The University of Sydney,
Sydney, N.S.W. 2006, Australia.